

Developmental Toxicity in the Rat After Ingestion or Gavage of Organophosphate Pesticides (Dipterex, Imidan) during Pregnancy

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The structural development of fetuses was altered when Dipterex was administered by diet to pregnant rats from days 6 through 15 of gestation. Major external and skeletal alterations occurred after consumption of 432 or 519 mg/kg body weight per day, only minor skeletal changes occurred in the 375 mg/kg dose group and the incidence of alterations in the 145 mg/kg dose group was not significantly different from that in the pair-fed controls. The malformations seen at the two highest doses did not result directly from the associated decrease in food consumed. Dipterex was not shown to have teratogenic potential when given for the same time span, once daily by gavage, even at levels that produced maternal lethality. Imidan was not teratogenic when similarly given, either by diet at concentrations that resulted in a 45% reduction in food consumption, or by gavage at dose levels that resulted in some maternal lethality. Data collected from pair-fed control females revealed that limitation of food consumption to 13-15 g/rat per day from days 6 through 15 of gestation did not result in increased fetal mortality or stunting. However, fetal weight was reduced slightly, and the incidence of minor skeletal changes was approximately three to four times that among fetuses of control dams that were not pair-fed.

Introduction

Dipterex (*O,O*-dimethyl-1-hydroxy-2,2,2-trichloroethylphosphonate) and Imidan *N*(mercapto-methyl)phthalimide *S*-(*O,O*-dimethylphosphorodithioate) are organophosphate insecticides that are widely used in the United States, the Soviet Union, and in many other countries. In spite of their extensive application, little information has been published regarding possible adverse effects of these chemicals upon the mammalian conceptus. Therefore, their teratogenic potential was studied in the rat by both Soviet and American investigators. The results of the initial studies conducted in the United States are presented in this article.

Materials and Methods

Nonparous, female rats (CD strain) weighing between 225 and 275 g were cohoused overnight with mature males of the same strain in quarters lighted for 12 hr of each day and maintained at 20°C (50% RH). Mating was confirmed by detection of spermatozoa in the vaginal lavage the following morning (day 1 of gestation). Between days 1 and 6 of gestation, all rats were caged individually and had free access to tap water and ground Wayne Lab Blox. On day 6 of gestation, the rats were randomly assigned to experimental or control groups, except that control rats to be pair-fed were individually selected to match their partner's weight as closely as possible. It was established by a preliminary study that female rats of the CD strain would generally consume about 25 g of food daily. Therefore, the insecticides were added to the diets so that the desired dose levels

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would be present in 23 g. From day 6 through day 17 of gestation all female rats (except pair-fed controls) were given 25 g of food per day; thereafter, until sacrifice on day 21 of gestation, food was provided *ad libitum*.

Dipterex (Lot 4050066, 98.5% pure, from Chemagro Corp.) and Imidan (Lot 673-124, 95.8% pure, from Stauffer Chemical Co.) were administered from day 6 through day 15 of gestation by gavage (in 10 ml/kg of 0.5% methylcellulose in water) or by addition to the diet. Dose levels tested for each agent ranged from those toxic to the dam or the fetus to those that appeared to be without effect on the conceptus by predetermined criteria. Dipterex was added to the diet to deliver 0, 75, 150, 400, or 600 mg/kg body weight per day (mg/kg-day); the average levels actually consumed were 0, 76, 145, 375, 432, and 519 mg/kg-day, respectively. Imidan was added to the diet similarly to deliver 0, 10, 25, 40, and 50 mg/kg-day; the average levels actually consumed were 0, 10, 22, 27, and 29 mg/kg-day, respectively. By gavage, Dipterex was administered at 50, 75, 150, 200, and 250 mg/kg-day and Imidan was administered at 5, 10, 20, 25, and 30 mg/kg-day; control females were gavaged with vehicle only. Additional females were pair-fed from day 6 through day 17 of gestation on a 1:1 basis to females given the larger doses of insecticide by diet or by gavage. Dietary mixtures were prepared twice per week, and suspensions for gavage were prepared daily. Food and chemicals were refrigerated from receipt till dispensed to the animals. The cardinal signs of each female were noted several times each day during the dosing period. The dams were weighed on days 1, 6, 8, 10, 12, 14, 15, 17, and 21 of gestation.

On day 21 of gestation, the rats were sacrificed by cervical dislocation and their reproductive status was determined. The implantation sites in each uterine horn were numbered consecutively, and the status of the conceptus at each site was recorded with respect to being alive or dead, and as to general condition. Only live fetuses were weighed, sexed, and examined for external malformations. Any live fetus weighing 2.0 g or less, or weighing less than two-thirds the average of its larger litter-mates, was termed "stunted". At least one-third of the fetuses of each litter were dissected to reveal visceral alterations (1). All stunted fetuses and those having external malformations also were examined for visceral alterations. Thereafter, all fetuses that were alive at the time of sacrifice were processed and examined for skeletal

alterations (2). The skeletons of all dead, but non-macerated, fetuses were examined: skeletal malformations obviously present before death were recorded routinely, but the information was not included in the tables presented here.

Nonparametric test procedures were employed in the data analysis. The litter was taken as the experimental unit and incidence data were expressed as mean percent affected fetuses per litter. Experimental groups were compared to controls by Mann-Whitney U tests (3) while Jonckheere's test (4) was employed to test the significance of dose-response relationships. The Wilcoxon signed-rank test (3) was used to compare animals given insecticide to the matched pair-fed controls. Rank analysis of covariance procedures (5) were employed to adjust fetal weight for differences in sacrifice time and number of live fetuses per litter. One-sided tests were employed and differences significant at the 0.05 level were noted.

Results

General

Pilot trials were conducted by gavage to determine the maximum dose level tolerated (MTD) by nonpregnant females. Among surviving female rats it was observed that the expected cardinal signs denoting cholinesterase inhibition were quite transitory after Dipterex administration. Rats given the highest doses of Dipterex would collapse for about 1 hr, during which period muscular tremors, ptalism, dacryorrhea, exophthalmia, and piloerection, occurred. These cardinal signs disappeared about 8 hr after dosing and occurred at about the same intensity daily during the dosing period; hence the effects were not cumulative. On the other hand, effects after Imidan administration tended to accumulate. Therefore, to have the animals survive the 10-day dosing period, it was necessary to administer a dose that did not induce adverse cardinal signs during the first four days of gavaging. As a result, despite the similarity of the reported acute oral LD₅₀ of the two compounds (500 versus 300 mg/kg, respectively) the maximum dose that was nonlethal after ten daily administrations differed quite markedly (75 versus 15 mg/kg-day, respectively). Even on day 6 of gestation, mated females were less susceptible to both compounds than were nonpregnant females. Due to these differences, the MTD calculated from studies on

nonpregnant females had to be increased for pregnant females, and considerably higher doses of Dipterex were tolerated than was the case with Imidan. Furthermore, the MTD by gavage once daily (i.d.) was substantially lower than the MTD by diet. The only cardinal signs noted among the dams given Dipterex by diet were decreased food intake and the associated decrease in body weight gain; for Imidan, piloerection and hyperirritability were also present.

The control rats for the groups given insecticide by diet ate only the base diet; the control rats for the groups administered insecticide by gavage were given the vehicle by gavage. Since the maternal and fetal response of these two control groups did not differ significantly for any of the criteria listed in Table 1, the data from these groups were combined. Five malformed fetuses were found among the 474 live fetuses obtained from the 44 control litters; these consisted of 4 fetuses with doubled vertebral centra and 1 with diaphragmatic hernia.

Dipterex Diet

Administration of Dipterex from day 6 through day 15 of gestation did not result in maternal deaths; however, dosage levels were increased until maternal food consumption and rate of gain were significantly reduced (Table 1). Reduction in consumption with 0.15 g of Dipterex added to each 23 g of food resulted in daily intake of 432 mg of Dipterex/kg rather than the intended 500 mg/kg; similarly, at the highest dose an actual level of 519 mg/kg was achieved instead of the intended 600 mg/kg. At sacrifice on day 21 of gestation fetal weight was significantly reduced in the two highest dose groups but fetal mortality was significantly increased only for the second highest dose group (432 mg/kg-day). A significant dose-related increase in the incidence of malformations occurred among the groups given Dipterex at 145 mg/kg-day or more. In the two highest dose groups, 109 fetuses were malformed. The malformations included 33 alterations of the skull and central nervous system (exencephaly, meningocoele, hydrocephaly), 26 of the limb (syndactyly, markedly shortened radii and ulnae, missing digits), 14 micrognathiae, 19 cleft palates, 9 facial hematomas, 17 cases of generalized edema, 11 fused sterna, 92 doubled vertebral centra, 7 wavy ribs, and four great vessel defects. There were seven other malformations that occurred only once.

In the 375 mg/kg-day group the defects detected were primarily minor skeletal alterations viz. 13 doubled vertebral centra, three wavy ribs, two fenestrated supraoccipital bones and one umbilical hernia. The few defects noted in the 145 mg/kg-day group occurred in five fetuses. The malformations consisted of three doubled vertebral centra, two fenestrated supraoccipital bones and one exencephaly. This slight increase in malformations, although significant relative to the control group, was not statistically significant relative to the incidence of malformed fetuses (2 of 108) detected in the pair-fed control group. Both malformed fetuses in the pair-fed group had doubled vertebral centra and one also had a fused sternum.

Dipterex Gavage

Dipterex was administered by gavage from day 6 through day 15 of gestation at dose levels that resulted in significant dose-related maternal mortality (150 mg/kg-day or more). Among the survivors the incidence of pregnancy tended to be decreased. Food consumption was decreased at least as much as it was when Dipterex was added to the diet. At the dose levels tested fetal mortality was not significantly increased, but the fetuses from dams given Dipterex at 75 mg/kg-day or more were significantly smaller than those from the control dams. In spite of the maternal and fetal toxicity associated with the high levels of Dipterex administered, a significant increase in malformations was not obtained. The overall incidence of malformations in these groups was only 2.5% among 640 fetuses from 54 litters. All of the observed defects were minor skeletal alterations: eleven doubled vertebral centra and three fenestrated skull bones.

Imidan Diet

Food intake was severely curtailed in the groups given Imidan at the higher dose levels. This placed a practical upper limit on the attainable dosage of Imidan consumed since increased concentration in the diet was virtually offset by reduced food consumption. Thus, the actual dose levels in the three highest dose groups were similar (Table 2). Maternal deaths were not observed at the dose levels attained, but food consumption was decreased by 45% and associated weight gain was reduced to essentially zero at the highest dose. Despite this level of maternal toxicity, fetal toxicity, as measured by mortality, the incidence of stunting, and fetal

Table 1. Effect of Dipterex administration by diet or gavage to CD rats from day 6 through day 15 of gestation.

	Diet						Gavage					
	0	76	145	375	432	519	50	75	150	200	250	
	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	
Females												
Total number	47	9	9	17	26	24	9	9	18	30	11	
Number dead (%)	0	0	0	0	0	0	0	0	3(17) ^a	6(20) ^a	7(64) ^a	
Number pregnant (%) ^b	44(94)	9(100)	9(100)	17(100)	21(81)	19(79)	9(100)	9(100)	13(87)	21(88)	2(50) ^a	
Food intake ^c	24 ± 0.2	23 ± 0.6	22 ± 0.7 ^a	22 ± 0.4 ^a	20 ± 0.5 ^a	20 ± 0.3 ^a	22 ± 0.6 ^a	21 ± 0.5 ^a	21 ± 0.4 ^a	20 ± 0.5 ^a	23 ± 0.6	
Weight gain, ^d	45 ± 1.9	53 ± 3.2	58 ± 5.1	40 ± 5.4	37 ± 2.6 ^a	27 ± 2.5 ^a	41 ± 6.9	42 ± 3.2	42 ± 3.4	42 ± 2.0	47 ± 7.0	
Fetuses												
Total number	474	117	118	181	216	180	98	120	159	242	21	
Fetal death, %	6 ± 1.8	2 ± 1.8	4 ± 2.4	6 ± 4.7	18 ± 5.5 ^a	10 ± 4.4	12 ± 8.1	5 ± 2.8	4 ± 2.0	3 ± 1.2	0	
Stunted, %	0	0	0	0	0.3 ± 0.3	0.5 ± 0.5	0	0	0	0	0	
Weight, g	4.0 ± .05	3.9 ± .08	3.8 ± .07	4.0 ± .16	3.5 ± .08 ^a	3.5 ± .12 ^a	3.9 ± .23	3.7 ± .07 ^a	3.8 ± .08 ^a	3.5 ± .07 ^a	2.3 ± .11 ^a	
Malformed, %	1 ± 0.5	0	4 ± 1.9 ^a	11 ± 3.7 ^a	30 ± 8.1 ^a	30 ± 9.2 ^a	4 ± 3.7	3 ± 1.9	3 ± 1.5	2 ± 1.2	0	

^ap < 0.05 compared to controls.^bAt least one resorption site *in utero* at sacrifice.^cAverage consumption per day from day 6 through day 15 of gestation (X ± SE).^dAverage weight change from day 6 through day 17 of gestation (X ± SE).

Table 2. Effect of Imidan administration by diet or by gavage to CD rats from day 6 through day 15 of gestation.

	Diet					Gavage				
	0	10	22	27	29	5	10	20	25	30
	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day
Females										
Total number	47	9	9	17	23	9	9	18	32	2
Number dead (%)	0	0	0	0	0	0	0	0	5(16) ^a	2(100) ^a
Number pregnant (%) ^b	44(94)	8(89)	9(100)	16(94)	23(100)	9(100)	9(100)	15(83)	19(70) ^a	—
Food intake ^c	24 ± 0.2	23 ± 0.6	20 ± 0.5 ^a	15 ± 0.6 ^a	13 ± 0.4 ^a	23 ± 0.6	22 ± 0.8 ^a	17 ± 0.8 ^a	15 ± 0.9 ^a	—
Weight gain, g ^d	45 ± 1.9	48 ± 4.8	38 ± 2.7 ^a	9 ± 4.0 ^a	-1 ± 4.5 ^a	53 ± 4.1	45 ± 2.9	19 ± 5.8 ^a	12 ± 5.4 ^a	—
Fetuses										
Number live	474	102	117	186	276	117	118	159	185	—
Fetal death, %	6 ± 1.8	0	1 ± 0.9	9 ± 2.7	4 ± 1.9	2 ± 1.2	1 ± 0.7	8 ± 3.2	8 ± 4.3	—
Stunted, %	0	0	0.8 ± 0.8	0	0	0	0	0	0	—
Weight, g	4.0 ± 0.05	4.0 ± 0.23	4.0 ± 0.10	4.0 ± 0.12	3.9 ± 0.06	3.7 ± 0.08 ^a	3.7 ± 0.10 ^a	3.5 ± 0.08 ^a	3.5 ± 0.15 ^a	—
Malformed, %	1 ± 0.5	1 ± 0.9	3 ± 1.8	1 ± 0.8	3 ± 1.4	0	1 ± 0.8	1 ± 0.7	2 ± 0.9	—

^a $p < 0.05$ compared to controls.^b At least one resorption site *in utero* at sacrifice.^c Average consumption per day from day 6 through day 15 of gestation ($X \pm SE$).^d Average weight change from day 6 through day 17 of gestation ($X \pm SE$).

weight, was not increased and insecticide-related malformations were not detected. The overall incidence was only 2.1% among 681 fetuses from 56 litters. Defects consisted of ten cases of doubled vertebral centra, two wavy ribs, and one fused sternum.

Imidan Gavage

Significant maternal mortality was noted after daily administration of Imidan at 25 or 30 mg/kg from day 6 through day 15 of gestation. Food consumption and body weight gain were severely inhibited, but unlike the case when Imidan was given in the diet, fetal weight was significantly reduced. However, even at dose levels that produced obvious maternal effects, the incidence of fetal mortality, stunted fetuses and malformations were not significantly increased. The overall incidence of structural alterations detected was only 1.0%. The changes noted among the six affected fetuses were five cases of doubled vertebral centra and one small kidney. None of the 1260 fetuses from 108 dams administered Imidan had any of the severe defects seen among the fetuses of the dams given Dipterex by diet.

Pair-Fed Controls

Data collected from pair-fed controls (Table 3) revealed that the reduction in maternal weight gain observed among the groups given Dipterex or Imidan by either route was no more pronounced than that achieved merely by comparable food restriction (Table 3). Furthermore, except for the increase obtained in the group given Dipterex by diet at 432 mg/kg (17.8%), the incidence of fetal mortality among the groups given either insecticide was not significantly greater than that seen among the pair-fed control groups.

Dose-related differences in fetal weight did occur between the groups given Imidan by gavage and the corresponding pair-fed groups. Fetal weights in two of the groups given Dipterex were significantly reduced relative to pair-fed controls, but these two groups were not the highest dose levels tested. The increased incidence of malformations seen among the offspring of the groups given Dipterex by diet at 375 mg/kg or more did not result solely from reduced food consumption by the dams.

Comparison of even the most severely restricted pair-fed control groups to control groups that were not pair-fed revealed no significant differences with

respect to fetal mortality or stunting. However, the fetuses from the pair-fed rats were smaller than fetuses from control dams and the incidence of malformed fetuses was slightly increased (2.3% versus 1.0%, respectively). Defects which occurred among 24 of 1218 fetuses from 108 pair-fed dams consisted of 19 doubled vertebral centra, three wavy ribs, and one fused centrum, one fused sternum, one mild hydrocephaly, one missing aortic arch, and one defective retina.

Dead Fetuses

Seven dead fetuses (not macerated) were examined for skeletal defects. The three from rats given Dipterex by diet (two in the 432 mg/kg and one in the 145 mg/kg dose group) each had doubled vertebral centra and one also had wavy ribs. The remaining four dead fetuses occurred in pair-fed control groups; a skeletal change was seen in only one fetus (fused lumbar arches).

Discussion

Major malformations that were pesticide-related occurred only in the fetuses of dams given the two highest concentrations of Dipterex in their diet. This teratogenic response probably was achieved only by the prolonged presence of Dipterex in the dam at a high concentration since neither lower doses in the diet nor single daily administration of maternally toxic doses by gavage resulted in major malformations. Whether similar malformations will result from multiple daily administration by gavage is under study. It is important to establish this point, particularly for chemicals designed for short duration of pharmacologic effect, since many chemicals have been administered only by gavage i.d. for determining their teratogenic potential or fetal toxicity.

Dipterex was found to have definite teratogenic potential in one species but only at doses that adversely affected maternal food consumption and at dose levels far in excess of expected levels of human exposure. Acceptable daily intake in man is reported to be 0.18 mg/kg (6). Hence, since the authors know of no other information on the effects of Dipterex on mammalian offspring, this chemical is not considered to represent a definite hazard to the human fetus. However, additional studies are being conducted.

Imidan was not found to be teratogenic in this study even after administration of doses lethal to

Table 3. Data from control rats pair-fed from day 6 through day 17 of gestation.

	Dipterex diet ^a						Dipterex gavage ^a				Imidan diet ^a		Imidan gavage ^a	
	145	432	519		75	200	250	22	29	10	25			
	mg/kg-day	mg/kg-day	mg/kg-day		mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day			
Females														
Total number	9	18	14		9	16	10	9	15	9	18			
Number dead (%)	0	0	2(14)		0	0	0 ^b	0	0	0	1(6)			
Number pregnant (%) ^c	9(100)	16(89)	11(92)		9(100)	16(100)	8(80)	7(78)	11(73)	7(78)	14(82)			
Food intake, g ^d	22 ± 0.7	20 ± 0.7	20 ± 0.7		21 ± 0.5	20 ± 0.5	21 ± 0.5	20 ± 0.7	13 ± 0.7	22 ± 0.8	15 ± 1.0			
Weight gain, g ^e	43 ± 1.6 ^b	28 ± 5.0	20 ± 3.9		38 ± 2.7	33 ± 3.2 ^b	20 ± 2.8	39 ± 5.0	6 ± 3.3	42 ± 4.6	7 ± 4.9			
Fetuses														
Number live	108	199	97		114	170	82	90	122	86	150			
Fetal death, %	5 ± 3.4	5 ± 2.1 ^b	13 ± 4.2		1 ± 0.7	12 ± 4.9	3 ± 1.4	8 ± 7.0	8 ± 3.5	3 ± 2.0	4 ± 1.9			
Stunted, %	1 ± 0.8	1 ± 0.5	0		0	0	0	1 ± 0.8	0	0	0			
Weight, g	3.8 ± 0.08	3.7 ± 0.08 ^b	3.6 ± 0.22		4.1 ± 1.0 ^b	3.7 ± 0.07	4.2 ± 0.23	3.9 ± 0.11	3.8 ± 0.11	4.0 ± 0.09 ^b	3.8 ± 0.11			
Malformed, %	2 ± 1.2	3 ± 1.2 ^b	2 ± 1.1 ^b		0	1 ± 0.7	6 ± 2.6	1 ± 0.8	3 ± 1.2	0	4 ± 2.1			

^aRefers to dose administered to corresponding experimental group.^b*p* < 0.05 compared to corresponding pair-fed experimental group.^cAt least one resorption site *in utero* at sacrifice.^dAverage consumption per day from day 6 through day 15 of gestation (X ± SE).^eAverage weight change from day 6 through day 17 of gestation (X ± SE).

the most sensitive dams and toxic to surviving dams. This finding is in contrast to the results obtained by our Soviet counterparts as published elsewhere in this issue (7). Many factors could conceivably contribute to minor differences in results between two laboratories. However, differences of the magnitude experienced in this case were considered most likely to be the result of administration of different chemicals; samples of the insecticides used in this study were given to our Soviet counterparts to determine whether this was the case. A second possibility, suggested by Dyban (A. R. Dyban, Dept. Embryology, Institute of Experimental Medicine, USSR Academy of Medical Science, Leningrad, USSR, personal communication), relates to differences in diet. This suggestion is the result of a study which demonstrated that rats fed a diet virtually identical to that used by our Soviet counterparts were unusually sensitive to thalidomide due to the presence of only borderline levels of the vitamin B complex (8). It is hoped the differences between laboratories with respect to the effect of Imidan administration will be resolved by additional investigation.

Studies known to the authors in which the effect of Imidan on the mammalian conceptus was investigated consist of one published article by Fabro et al. (9) and three unpublished reports kindly supplied by the Stauffer Chemical Company. Fabro et al. (9) administered Imidan, obtained from England, to five rabbits from day 7 through day 12 of pregnancy at 35 mg/kg-day which was the MTD. No adverse effects were noted among the offspring. In the unpublished reports Imidan was added to the diet of weanling rats of both sexes at 40 or 80 ppm through three generations. Adverse effects were not demonstrated at these levels of administration. Similarly, no adverse effects were noted in the reproductive performance of the adults or among the offspring of female rabbits (12 dose/group) administered Imidan in the diet at 10, 30, or 60 mg/kg body weight/day from three weeks before mating through day 18 of gestation. In addition, Imidan was administered orally to 21 rhesus

monkeys on day 22 through day 32 of gestation at 2, 4, or 8 mg/kg (seven females per group). Malformations were not noted among the 18 fetuses examined on Day 84 of gestation; two of the concepti from the low dose group and one from the high dose group either aborted or were resorbed. Before use in this study all 59 adult female monkeys had at least one live baby; two of the females also had prior abortions.

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